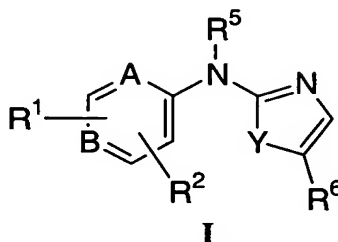


WHAT IS CLAIMED IS:

1. A compound of Formula I



- 5 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

A and B are independently N or N⁺—O⁻;

Y is O, S or N-R⁴;

10

R¹ and R² are independently:

- 1) H,
- 2) O_r(C₁-C₆)perfluoroalkyl,
- 3) OH,
- 15 4) CN,
- 5) halogen,
- 6) (C=O)_rO_s(C₁-C₁₀)alkyl,
- 7) (C=O)_rO_s(C₂-C₁₀)alkenyl,
- 8) (C=O)_rO_s(C₂-C₁₀)alkynyl,
- 20 9) (C=O)_rO_saryl,
- 10) (C=O)_rO_sheterocyclyl,
- 11) (C₀-C₆)alkyl-NR^aR^b, or
- 12) (C₁-C₆)heterocyclyl,

wherein r and s are independently 0 or 1, and said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl is optionally substituted with one or more substituents selected from R⁷;

R⁴ is H, aryl or (C₁-C₆)alkyl;

5

R⁵ is:

- 1) H,
- 2) SO₂R^c,
- 3) (C=O)_rR^c, wherein r is 0 or 1, or
- 10 4) CO₂R^c;

R⁶ is:

- 1) aryl,
- 2) CN,
- 15 3) halogen,
- 4) (C=O)NR^aR^b,
- 5) (C₁-C₁₀)alkyl,
- 6) (C₂-C₈)alkenyl,
- 7) (C₂-C₈)alkynyl, or
- 20 8) heterocyclyl,

wherein r and s are independently 0 or 1, and said aryl, alkyl, alkenyl, alkynyl and heterocyclyl optionally substituted with one or more substituents selected from R⁷;

R⁷ is:

- 25 1) O_r(C=O)_sNR^aR^b,
- 2) (C=O)_rO_saryl,
- 3) (C=O)_rO_s-heterocyclyl,
- 4) halogen,

- 5) OH,
 6) oxo,
 7) O(C₁-C₃)perfluoroalkyl,
 8) (C₁-C₃)perfluoroalkyl,
 5 9) (C=O)_rO_s(C₁-C₆)alkyl,
 10) CHO,
 11) CO₂H,
 12) CN,
 13) (C₁-C₆)alkyl-NR^aR^b, or
 10 14) (C₁-C₆)alkyl-heterocyclyl,

wherein r and s are independently 0 or 1, and said aryl, heterocyclyl and alkyl are optionally substituted with one to three substituents selected from R^d;

R^a and R^b are independently

- 15 1) H,
 2) (C=O)_r(C₁-C₁₀)alkyl,
 3) S(O)₂R^c,
 4) (C=O)_rheterocyclyl,
 5) (C=O)_raryl, or
 20 6) CO₂R^c,

wherein r is 0 or 1 and said alkyl, heterocyclyl, and aryl optionally substituted with one or more substituents selected from R^d, or

- R^a and R^b are taken together with the nitrogen to which they are attached to form a
 25 monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^d;

R^c is (C₁-C₆)alkyl, aryl, or heterocyclyl; and

R^d is:

- 5 1) (C=O)_rO_s(C₁-C₁₀)alkyl, wherein r and s are independently 0 or 1,
 optionally substituted with up to three substituents selected from OH,
 (C₁-C₆)alkoxy, halogen, heterocyclyl, CN, oxo, N(R^e)₂ and S(O)₂R^c,
- 2) O_r(C₁-C₃)perfluoroalkyl,
- 3) (C₀-C₆)alkylene-S(O)_mR^c, wherein m is 0, 1, or 2,
- 10 4) oxo,
- 5) OH,
- 6) halo,
- 7) CN,
- 8) (C₀-C₆)alkylene-aryl, optionally substituted with up to three
- 15 substituents selected from R^e,
- 9) (C₀-C₆)alkylene-heterocyclyl, optionally substituted with up to three
- substituents selected from R^e,
- 10) C(O)R^c,
- 11) CO₂R^c,
- 20 12) C(O)H,
- 13) N(R^e)₂, or
- 14) CO₂H;

R^e is:

- 25 1) H,
- 2) (C₁-C₆)alkyl, optionally substituted with one or more substituents
 selected from OH, heterocyclyl, (C₁-C₆)alkoxy, halogen, CN, oxo,
 N(R^f)₂ and S(O)₂R^c,

- 3) aryl, optionally substituted with one or more substituents selected from OH, heterocyclyl, (C₁-C₆)alkoxy, halogen, CN, N(R^f)₂ and S(O)₂R^c,
 4) heterocyclyl, optionally substituted with one or more substituents selected from OH, heterocyclyl, (C₁-C₆)alkoxy, halogen, CN, oxo,
 5 N(R^f)₂ and S(O)₂R^c, or
 6) S(O)₂R^c, or

if two R^e's are on a nitrogen atom, they can be taken together with the nitrogen to form a heterocycle with 5-7 atoms, optionally containing, in addition to the nitrogen,
 10 one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from OH, (C₁-C₆)alkoxy, halogen, CN, oxo, N(R^f)₂ and S(O)₂R^c; and

R^f is H, aryl or (C₁-C₆)alkyl.

15

2. The compound of Claim 1, wherein

Y is S;

20

R¹ is H, (C₁-C₆)alkyl, or O(C₁-C₆)alkyl;

R² is:

- 25 1) H, provided that both R¹ and R² are not H at the same time,
 2) O_T(C₁-C₆)perfluoroalkyl,
 3) OH,
 4) CN,
 5) halogen,

- 5
- 6) $(\text{C}=\text{O})_r\text{O}_s(\text{C}_1\text{-C}_{10})\text{alkyl}$,
 - 7) $(\text{C}=\text{O})_r\text{O}_s(\text{C}_2\text{-C}_{10})\text{alkenyl}$,
 - 8) $(\text{C}=\text{O})_r\text{O}_s(\text{C}_2\text{-C}_{10})\text{alkynyl}$,
 - 9) $(\text{C}=\text{O})_r\text{O}_s\text{aryl}$,
 - 10) $(\text{C}=\text{O})_r\text{O}_s\text{heterocyclyl}$,
 - 11) $(\text{C}_0\text{-C}_6)\text{alkyl-NR}^a\text{R}^b$, or
 - 12) $(\text{C}_1\text{-C}_6)\text{heterocyclyl}$,

wherein r and s are independently 0 or 1, and said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl is optionally substituted with one or more substituents selected from R^7 ;

10

R^6 is:

- 15
- 1) aryl,
 - 2) CN,
 - 3) halogen,
 - 4) $(\text{C}=\text{O})\text{NR}^a\text{R}^b$,
 - 5) $(\text{C}_1\text{-C}_6)\text{alkyl}$,
 - 6) $(\text{C}_2\text{-C}_6)\text{alkenyl}$,
 - 7) $(\text{C}_2\text{-C}_6)\text{alkynyl}$, or
 - 8) heterocyclyl,

20 wherein r and s are independently 0 or 1, and said aryl, alkyl, alkenyl, alkynyl and heterocyclyl optionally substituted with one to three substituents selected from R^7 ;

R^7 is:

- 25
- 1) $\text{O}_r(\text{C}=\text{O})_s\text{NR}^a\text{R}^b$,
 - 2) $(\text{C}=\text{O})_r\text{O}_s\text{aryl}$,
 - 3) $(\text{C}=\text{O})_r\text{O}_s\text{-heterocyclyl}$,
 - 4) halogen,
 - 5) OH,

- 5
- 6) oxo,
 - 7) O(C₁-C₃)perfluoroalkyl,
 - 8) (C₁-C₃)perfluoroalkyl,
 - 9) (C=O)_rO_s(C₁-C₆)alkyl,
 - 10) CHO,
 - 11) CO₂H,
 - 12) CN,
 - 13) (C₁-C₆)alkyl-NR^aR^b, or
 - 14) (C₁-C₆)alkyl-heterocyclyl,

10 wherein r and s are independently 0 or 1, and said aryl, heterocyclyl and alkyl are optionally substituted with one to three substituents selected from R^d;

R^a and R^b are independently:

- 15
- 1) H,
 - 2) (C=O)_r(C₁-C₁₀)alkyl,
 - 3) S(O)₂R^c,
 - 4) (C=O)_rheterocyclyl,
 - 5) (C=O)_raryl, or
 - 6) CO₂R^c,

20 wherein r is 0 or 1 and said alkyl, heterocyclyl, and aryl optionally substituted with one or more substituents selected from R^d, or

25 R^a and R^b are taken together with the nitrogen to which they are attached to form a monocyclic 5-7 membered heterocycle optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one to three substituents selected from R^d; and

R^d is:

- 1) $(C=O)_rO_s(C_1-C_6)alkyl$, wherein r and s are independently 0 or 1, optionally substituted with up to three substituents selected from OH, $(C_1-C_6)alkoxy$, halogen, CN, oxo, $N(R^e)_2$ and $S(O)_2R^c$,
- 2) $O_r(C_1-C_3)perfluoroalkyl$,
- 5 3) $(C_0-C_6)alkylene-S(O)_mR^c$, wherein m is 0, 1, or 2,
- 4) oxo,
- 5) OH,
- 6) halo,
- 7) CN,
- 10 8) $(C_0-C_6)alkylene-aryl$, optionally substituted with up to three substituents selected from R^e ,
- 9) $(C_0-C_6)alkylene-heterocyclyl$, optionally substituted with up to three substituents selected from R^e ,
- 10) $(C_0-C_6)alkylene-N(R^e)_2$,
- 15 11) $C(O)R^c$,
- 12) CO_2R^c ,
- 13) $C(O)H$, or
- 14) CO_2H .

20 3. The compound of Claim 2, wherein A and B are N; and R^6 is phenyl, halogen, CN, or pyridyl said phenyl and pyridyl optionally substituted with one to three substituents selected from R^7 .

25 4. The compound of Claim 3 wherein R^1 is H and R^2 is $O_r(C_1-C_6)alkyl$, wherein r is 0 or 1, optionally substituted with one to three substituents selected from R^7 , or $(C_0-C_6)alkyl-NR^aR^b$.

5. A compound selected from:

2-({6-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

2-({6-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

5 *N*-(*tert*-butyl)-2-(4-{6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}piperazin-1-yl)acetamide;

2-({6-[4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

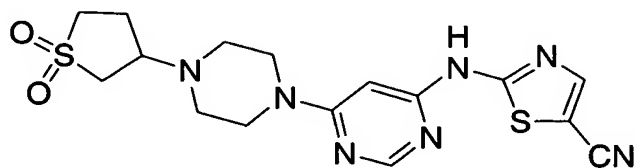
2-(4-{6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}piperazin-1-yl)-*N*-isopropylacetamide;

2-(1-{6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}piperidin-4-yl)-*N*-isopropylacetamide; and

2-({6-[4-(2-oxopiperidin-3-yl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile; or a pharmaceutically acceptable salt or stereoisomer thereof.

15

6. A compound which is 2-({6-[4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile

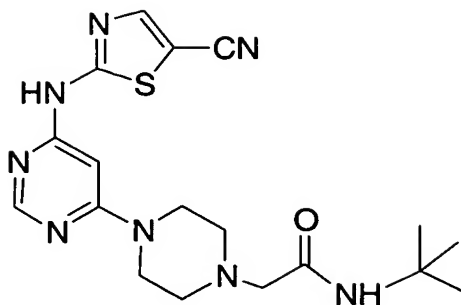


20

or a pharmaceutically acceptable salt or stereoisomer thereof.

7. A compound which is *N*-(*tert*-butyl)-2-(4-{6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}piperazin-1-yl)acetamide

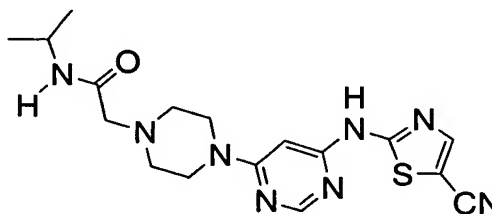
25



or a pharmaceutically acceptable salt thereof.

- 5 8. A compound which is the (R) or (S) enantiomer of 2-({6-[4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile in enantiomerically pure form as characterized by an enatiomeric excess of at least 98%, or a pharmaceutically acceptable salt thereof.

- 10 9. A compound which is 2-(4-{6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}piperazin-1-yl)-N-isopropylacetamide



- 15 or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition which is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

- 20 11. A method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Claim 1.

12. A method of treating cancer or preventing cancer in accordance with Claim 11 wherein the cancer is selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

5

13. A method of treating or preventing cancer in accordance with Claim 11 wherein the cancer is selected from histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma.

10

14. A method of treating or preventing cancer in accordance with Claim 11 wherein the cancer is selected from colorectal cancer, prostate cancer, breast cancer, and lung cancer.

15

15. A method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

20

16. A method in accordance with Claim 15 wherein the disease is an ocular disease.

25

17. A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Claim 1.

18. A method of treating or preventing diabetic retinopathy which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Claim 1.

19. A method of treating or preventing age-related macular degeneration which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.
- 5 20. The method of Claim 15 further comprising the use of photodynamic therapy with a photosensitive drug.
21. The method of Claim 20 wherein the photosensitive drug is verteporfin.
- 10 22. The method of Claim 20 wherein the disease is age-related macular degeneration.
23. A method of treating or preventing inflammatory diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.
- 15 24. A method according to Claim 23 wherein the inflammatory disease is selected from rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions.
- 20 25. A method of treating or preventing a tyrosine kinase-dependent disease or condition which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 25 26. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

27. A process for making a pharmaceutical composition which comprises combining a compound of Claim 1 with a pharmaceutically acceptable carrier.

5 28. A method of treating or preventing bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets which comprises administering a therapeutically effective amount of a compound of Claim 1.

10 29. The composition of Claim 10 further comprising a second compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 15 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 9) a reverse transcriptase inhibitor,
- 20 10) another angiogenesis inhibitor, and
- 11) a PPAR- γ agonist..

30. The composition of Claim 29, wherein the second compound is another angiogenesis inhibitor selected from the group consisting of a tyrosine kinase
25 inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-(chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an
30 antibody to VEGF.

31. The composition of Claim 29, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

5 32. The composition of Claim 10 further comprising a steroidal anti-inflammatory compound.

33. The composition of Claim 10 further comprising an anti-hypertensive compound.

10

34. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

15 35. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with an agent selected from:

- 20
- 1) an estrogen receptor modulator,
 - 2) an androgen receptor modulator,
 - 3) retinoid receptor modulator,
 - 4) a cytotoxic agent,
 - 5) an antiproliferative agent,
 - 6) a prenyl-protein transferase inhibitor,
 - 7) an HMG-CoA reductase inhibitor,
 - 25 8) an HIV protease inhibitor,
 - 9) a reverse transcriptase inhibitor, and
 - 10) another angiogenesis inhibitor.

36. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy and an agent selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 9) a reverse transcriptase inhibitor, and
- 10) another angiogenesis inhibitor.

37. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.

38. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a GPIIb/IIIa antagonist.

39. The method of Claim 38 wherein the GPIIb/IIIa antagonist is tirofiban.

40. A method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of Claim 1.

41. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.
- 5 42. A method of treating or preventing preeclampsia which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 10 43. A method of treating or preventing tissue damage due to bacterial meningitis which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 15 44. A method to treat or prevent endometrioses which comprises administering a therapeutically effective amount of a compound of Claim 1.
45. A method of treating or preventing diabetic retinopathy which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a PPAR- γ agonist.
- 20 46. A method of treating acute myeloid leukemia which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 25 47. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with gene therapy.